Remarks

Amendments to the Claims

The amendments to the claims delete subject matter or make minor corrections of form. The amendments add no new matter to the specification.

The Objection to Claims 8, 9, 10, 12, 13, 14, and 15

Claims 8, 9, 10, 12, 13, 14, and 15 are objected to under 37 C.F.R. § 1.75(c) as being in improper format. Claims 8 and 12 are canceled. Claims 9, 10, 13, and 14 are amended to eliminate objectionable multiple dependencies; the amendment to claim 14 also addresses the objection to dependent claim 15.

Applicants respectfully request withdrawal of the objection.

The Rejection of Claims 1-3 and 8-15 Under 35 U.S.C. § 112, second paragraph

Claims 1-3 and 8-15 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Claims 8 and 12 are canceled. Applicants respectfully traverse the rejection of independent claim 1 and dependent claims 2, 3, 9-11, and 13-15.

The Office Action asserts that the term "HML-2" is indefinite. Independent claim 1 has been amended to recite a "human endogenous MMTV-like subgroup 2 (HML-2) retrovirus." This amendment adds no new matter and is supported on page 35, line 16: "HML-2 is a subgroup of the HERV-K family [146]." "HML-2" is a well known designation for this subgroup. *See, e.g.*, the abstract of cited reference 146 (Attachment 1).

Applicants respectfully request withdrawal of the rejection.

The Rejections of Claims 1-15 Under 35 U.S.C. § 112, first paragraph

Claims 1-15 stand rejected under 35 U.S.C. § 112, first paragraph, as insufficiently described and as not enabled. Claims 8 and 12 are canceled. Applicants respectfully traverse the rejections of independent claim 1 and dependent claims 2, 3, 9-11, and 13-15.

Written Description

Independent claim 1 is directed to a method for diagnosing prostate cancer which involves detecting the presence or absence of an expression product of a human endogenous MMTV-like subgroup 2 (HML-2) retrovirus in a patient sample. Dependent claim 2 recites that the expression product is an RNA or a polypeptide. Dependent claim 3 recites that the patient sample is a prostate sample or a blood sample. Dependent claims 4-7 recite RNA products comprising particular sequences. Dependent claims 9 and 10 recite detection of a polypeptide product. Dependent claims 11 and 12 recite additional method steps (claim 11, obtaining the sample; claim 12, enriching RNA in the sample). Dependent claims 14 and 15 recite particular detection methods.

The first paragraph of 35 U.S.C. § 112 requires that the specification provide a written description of the claimed invention:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing

date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991).

As an initial matter, the Office Action asserts that the specification does not adequately describe a genus of polynucleotides "defined only by sequence identity." To advance prosecution, dependent claim 4 has been amended to delete recitations of percent identity. As amended, dependent claims 4-7 each recite a particular nucleotide sequence that is described in the specification; thus, at a minimum, the rejection should not apply to these claims.

The specification also adequately describes the subject matter of amended claims 1-3, 9-11, and 13-15. The specification need describe in detail only that which is "new or not conventional in the art." M.P.E.P. § 2163(II)(A)(3)(a), citing *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 U.S.P.Q. (BNA) 81, 94 (Fed. Cir. 1986). The recited HML-2 retroviral expression product is not a new or unconventional element in the art. Retroviruses of the HML-2 group were well known in the art at the December 7, 2000 priority date of this application. The specification teaches that HML-2 is a subgroup of the HERV-K family, citing Andersson *et al.*, *J. Gen. Virol. 80*, 255-60, 1999. Specification at page 36, line 16. The specification teaches that the K family of human endogenous retroviruses and its expression products are well known. See page 34, lines 13-26 and references cited therein. The specification also teaches that:

> HERV isolates which are members of the HML-2 subgroup include HERV-K10 [137, 142], the 27 HML-2 viruses shown in Figure 4 of reference 147, HERV-K(C7) [148], HERV-K(II) [145], HERV-K(CH). Table 11 provides a list of all known members of the HML-2 subgroup of the HERV-K family as determined by searching the Double-Twist database containing all genomic contigs with the sequence AF074086 using the Smith-Waterman algorithm with the default parameters: open gap penalty = -20 and extension penalty = -5.

Page 35, lines 16-22. The specification teaches that, because the HML-2 group is a well-recognized retroviral family, the skilled worker can readily recognize members of this family. Page 35, lines 24-26. Thus, their RNA and polypeptide expression products also are easily recognized. The specification also provides numerous examples of HML-2 expression products at page 36, line 1, to page 47, line 24.

The Office Action cites *Regents of the University of California v. Lilly*, *Fiers v. Revel*, *Amgen Inc. v. Chugai*, and *Fiddes v. Baird* to support the rejection. These cases addressed what is required for a written description or conception of new genetic material. Applicants are not claiming new genetic material *per se*. Applicants are claiming methods which involve detection of expression products of a group of retroviruses well known in the art. Thus, the Office Action's reliance on the cited cases is misplaced.

The specification must be considered as a whole when determining whether the written description requirement is met. *In re Wright*, 866 F.2d 422, 425, 9 U.S.P.Q.2d (BNA) 1649, 1651 (Fed. Cir. 1989). As a whole, the specification adequately describes the subject matter of claims 1-3, 9-11, and 13-15. Applicants therefore respectfully request withdrawal of the rejection.

Enablement

The legal test for whether a disclosure provides adequate enablement for a generic claim is that "the scope of the claims must bear a *reasonable correlation* to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970) (emphasis added). To evaluate the scope of enablement provided by a specification, the proper standard is whether any experimentation that

may be needed to practice the claimed invention by the skilled artisan is undue or unreasonable. *In re Wands*, 858 F.2d at 736-37, 8 U.S.P.Q.2d (BNA) at 1404 (Fed. Cir. 1988).

Independent claim 1 is directed to a method for diagnosing prostate cancer which involves detecting the presence or absence of an expression product of a human endogenous MMTV-like subgroup 2 (HML-2) retrovirus in a patient sample. The specification provides sufficient information to enable one skilled in the art to practice the method of independent claim 1 as well as the methods of dependent claims 2, 3, 9-11, and 13-15.

What is required is that "reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d at 1366, 42 U.S.P.Q.2d (BNA) at 1005 (Fed. Cir. 1997). As discussed above in connection with the written description of the invention, retroviruses of the HML-2 group and their RNA and polypeptide expression products were well known in the art at the December 7, 2000 priority date of this application. See page 34, lines 13-26 and references cited therein; page 35, lines 16-22; page 35, lines 24-26. In addition, the specification provides many examples of HML-2 polynucleotide sequences and polypeptides. See page 36, line 1, to page 47, line 24. The specification also contains an extensive discussion of methods by which to carry out the detection of the recited expression products. *See, e.g.*, page 8, line 16, to page 10, line 4; page 14, lines 7-32; and page 16, line 21, to page 28, line 1. *See also* page 69, line 1, to page 81, line 12. These teachings of the specification are sufficient to enable the claimed methods.

The Office Action asserts that the specification does not enable detection of nucleotide sequences "that are 50-80% sequence identical to the particular claimed SEQ ID NO: 155 and 5 sequences." Office Action at page 7, lines 4-5. To advance prosecution, recitations of percent

sequence identity have been deleted. At a minimum, the rejection should not apply to claims 4-7, which recite specific nucleotide sequences.

The Office Action also asserts that "applicants have not provided sufficient showing that an increase in the HML-2 level in the blood correlates with only prostate cancer." Office Action at page 7, lines 10-12. The Office Action speculates that an increased level of [a detection product of] an HML-2 retrovirus in the blood "could be due to pathologies found in the kidney or placenta." *Id.*, lines 13-14. The Office Action provides no supporting evidence for the speculation. Moreover the specification clearly defines "diagnosis" as encompassing a screening process: " 'diagnosis' according to the invention can range from a definite clinical diagnosis of disease to an indication that the patient should undergo further testing which may lead to a definite diagnosis. For example, the method of the invention can be used as part of a screening process, with positive samples being subjected to further analysis." Page 24, lines 16-19. Thus, even if *arguendo* the Office Action's speculation were true, the occurrence of increased HML-2 expression products in the blood need not correlate solely with prostate cancer.

The scope of claims 2, 3, 9-11, and 13-15 bears a reasonable correlation to the scope of enablement in the present specification. Thus, the specification meets the enablement requirement of 35 U.S.C. § 112, first paragraph.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 1-3 and 11 Under 35 U.S.C. § 102(a)

Claims 1-3 and 11 stand rejected under 35 U.S.C. § 102(a) as anticipated by Wang-Johanning *et al.*, *Amer. Assoc. Cancer Res. 40*, 424, abstract no. 2801, March 1999 ("Wang-Johanning"). Applicants respectfully traverse the rejection.

To reject a claim as anticipated, each and every element as set forth in the claim must be either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d (BNA) 1051, 1053 (Fed. Cir. 1987). Wang-Johanning does not meet this standard.

Independent claim 1 recites a method for diagnosing prostate cancer comprising detecting the presence or absence of an expression product of a human endogenous MMTV-like subgroup 2 (HML-2) retrovirus in a patient sample. Dependent claim 2 recites that the expression product is an RNA or a polypeptide. Dependent claim 3 recites that the patient sample is a prostate sample or a blood sample. Claim 11, which now is dependent on claim 1, recites a further step of obtaining the patient sample.

Wang-Johanning is cited as teaching "detection of human endogenous retrovirus envelope which is expressed at high levels in prostate cancer tissue." Office Action at page 8, last paragraph. Wang-Johanning teaches that one particular human endogenous retrovirus envelope, HERV-E 4-1, "is detected and highly expressed as mRNA in prostate cancer tissues, compared to normal prostate tissue or tissue from patients with other prostate disorders." An HML-2 retrovirus is not an HERV-E retrovirus. The specification teaches that "HML-2 is a subgroup of the HERV-K family." Page 35, line 16, internal reference omitted. HERV-K and HERV-E are separate retroviral families. See the abstract of Johnston *et al.*, Ann Neurol. 2001

Oct;50(4):434-42 (Attachment 2). Wang-Johanning contains no teaching relating overexpression of HML-2 expression products and prostate cancer.

Wang-Johanning does not anticipate the subject matter of claims 1-3 or 11. Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 1-7 and 11 Under 35 U.S.C. § 103(a)

Claims 1-7 and 11 stand rejected under 35 U.S.C. § 103(a) as obvious over Wang-Johanning and Barbulescu *et al.*, *Current Biol.*, August 1999 ("Barbulescu"). Applicants respectfully traverse the rejection.

The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness. The *prima facie* case requires three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8th ed., § 2142. In the present application, a *prima facie* case that claims 1-7 and 11 are obvious has not been made because there would have been no motivation for the ordinary artisan to have combined the teachings of the cited references.

Independent claim 1 recites detecting the presence or absence of an expression product of a human endogenous MMTV-like subgroup 2 (HML-2) retrovirus in a patient sample. Wang-Johanning is cited as teaching "detection of human endogenous retrovirus envelope, which is expressed at high levels in prostate cancer tissue." Office Action at page 9, last paragraph. Barbulescu is cited as teaching a full-length HERV-k108 sequence comprising SEQ ID NO:5

and SEQ ID NO:155. Office Action at page 10, first full paragraph. The Office Action asserts it would have been obvious "to utilize the detection method disclosed by Wang-Johannson et al. which is directed to HERV sequences and apply the sequences set out in Barbulescue et al." Office Action at page 10, lines 6-7.

In assessing obviousness, the teachings of the cited references must be considered as a whole and compared with the subject matter of the rejected claims. *Graham v. John Deere* 383 U.S. 1, 17 (1966). As discussed above, Wang-Johanning contains no teaching relating overexpression of HML-2 expression products and prostate cancer; thus, Wang-Johanning would not have motivated the ordinary artisan to have combined its teachings with those of Barbulescu. Barbulescu merely teaches detection of HERV-K viral sequences in humans; it contains no teaching relating overexpression of any HERV-K viral sequences with prostate cancer. Thus, nothing in Barbulescu would have motivated the ordinary artisan to have combined its teachings with those of Wang-Johanning.

The Office Action cites no motivation at all for making the combination. The Office Action has merely selected isolated elements of the two references and pieced them together using Applicants' specification as a template. This exercise is improper:

> [s]tatements [in a prior art reference] cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection cannot be predicated on the mere identification in [the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Kotzab, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d (BNA) 1313, 1317 (Fed. Cir. 2000). The Office Action has not established a sufficient motivation for the ordinary artisan to have

combined the cited teachings of Wang-Johanning and Barbulescu. Thus, there is no *prima facie* case of obviousness.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
BANNER & WITCOFF, LTD.

Date: August 4, 2004

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Attachment 1

1: AIDS Res Hum Retroviruses. 1996 Jun 10;12(9):833-40. Related Articles, Linl

Differential expression of human endogenous retroviral sequences similar to mouse mammary tumor virus in normal peripheral blood mononuclear cells.

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Mouse mammary tumor virus (MMTV) is a retrovirus that causes breast cancer in certain strains of mice. In a previous study we identified, by sequencing clones from human lymphocytes, six groups with similarities to MMTV. Using a primer pair derived from pol sequences conserved within types A, B, and D retroviruses and probes from the six human MMTV-like (HML-1 to HML-6) groups in an internally controlled hybridization assay w investigated the normal variation of expression in PBMCs. Variations occurred within all groups but was most significant within group HML-1, where hybridization signals differed by more than 500-fold between individuals. Groups HML-2 and HML-3 showed consistently stronger hybridization signals than groups HML-1 and HML-5, while group HML-6 resulted in weak signals for all individuals. Stringent hybridization of the amplified cDNA to 20 individual HML clones also demonstrated a marked heterogeneity of expression. Hybridization signals from some groups and sequences were found to be correlated, either in a positive or negative fashion. RNA isolated from PBMCs collected from two donors at four different time points (in the morning and in the afternoon on the same day, repeated 1 week later) was also analyzed using the six hml probes. A small variation in hybridization signals was seen in samples collected on the same day, but a larger difference was observed in samples taken 1 week later. The correlations and the differences in the expression of HMLs between individuals implicate a complex transcriptional regulation system of these sequences.

PMID: 8738436 [PubMed - indexed for MEDLINE]

Attachment 2

Comment in:
- Ann Neurol. 2001 Oct;50(4):429-30.

Monocyte activation and differentiation augment human endogenous retrovirus expression: implications for inflammatory brain diseases.

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Human endogenous retroviruses (HERVs) have been implicated as causative agents in diseases characterized by inflammation and macrophage activation, such as multiple sclerosis. Because monocyte activation and differentiation influence retroviral transcription and replication, we investigated the contribution of these processes to the expression of four HERV families (HERV-W, HERV-K, HERV-E, and HERV-H) in human monocytes, and autopsied brain tissue from patients with brain diseases associated with increased macrophage activity. Reverse transcriptase-polymerase chain reaction analysis of primary macrophages and U937 monocytoid cells stimulated with phorbol-12-myristate-13-acetate or lipopolysaccharide revealed three- to ninefold increases in HERV-W, HERV-K, and HERV-H RNA levels. In addition, elevated reverse transcriptase activity and HERV RNA were detectable in supernatants from PMA-stimulated U937 cultures, properties that could be attenuated with the inhibitor of monocyte differentiation threonine-lysine-proline. In contrast, stimulation of monocyte: decreased or had no effect on HERV-E expression. Compared with controls, HERV-W and HERV-K expression was increased in brain tissue from patients with multiple sclerosis or human immunodeficiency virus infection (AIDS, with concomitant elevated tumor necrosis factor-alpha levels. Similarly, elevated HERV-W levels were detected in patients with Alzheimer's dementia only when tumor necrosis factor-alpha expression was also evident (2 of 6 cases). The detection of several HERVs in inflammatory brain diseases and the capacity to augment HERV expression in monocytes with compounds that influence cellular activity suggest that increased expression of these viruses is a consequence of increased immune activity rather than causative of distinct diseases.